TAB 34

Drugs

Questions and Answers About FDA's Enforcement Action Against Unapproved Injectable Colchicine Products

1. What action is FDA taking concerning injectable drugs containing colchicine?

The U.S. Food and Drug Administration (FDA) has ordered companies to stop marketing unapproved drug products that contain colchicine in an injectable dosage form. Injectable colchicine is used for the intravenous administration of the drug. The action does not affect colchicine tablets, and they will remain on the market at this time. FDA took this action as part of its effort to ensure that all drugs marketed in the United States have the required FDA approval and that they are safe, effective, of good quality, and appropriately labeled. Individuals and firms must stop making these products within 30 days and stop shipping the product within 180 days. After these dates, all injectable colchicine drug products must have FDA approval to be manufactured or shipped interstate.

2. What is colchicine?

Colchicine is a drug with anti-inflammatory properties that is most commonly used for the treatment of gout. The oral dosage form of colchicine is typically used to prevent gout attacks. Colchicine for injection has been available in the United States since the 1950s and administered intravenously for the treatment of acute attacks of gout. Due to serious toxicities associated with the use of intravenous colchicine and the emergence of safer alternative therapies, intravenous colchicine is rarely used in current practice for acute gout treatment.

3. Why is FDA taking this action?

Drug products containing colchicine for intravenous use have been marketed without approval. Colchicine is a drug which, when not properly dosed, can produce harmful or fatal effects including abdominal pain, vomiting, seizures, lack of blood cell production, and organ failure. Because injectable colchicine is a toxic drug, and also a drug with a narrow margin between an effective dose and a toxic dose, proper manufacturing and dosing recommendations are essential. These can only be assured by making certain that the products are held to the rigorous safety and efficacy standards of the FDA approval process. This action affects all injectable colchicine products, as none currently have FDA approval. There was one manufacturer of injectable colchicine, but that firm voluntarily discontinued manufacture of injectable colchicine in October 2007.

4. What risks are associated with injectable colchicine-containing drugs?

Serious safety concerns, including fatalities, associated with intravenous colchicine drug products are well-documented in the literature and in adverse drug events reported to the agency. FDA is aware of 50 reports of adverse events associated with intravenous (i.v.) colchicine use, including 23 deaths, through June 2007. Three of these deaths occurred in March and April of 2007 and were associated with the use of compounded i.v. colchicine. Among the commonly reported events were neutropenia (low number of white blood cells), acute renal (kidney) failure, thrombocytopenia (low number of platelets), congestive heart failure, and pancytopenia (low number of all types of blood cells). Many of these adverse events are caused by colchicine toxicity, which can have serious and potentially fatal consequences.

As mentioned, colchicine is known to have a narrow therapeutic index, or a narrow margin of safety between doses that are therapeutic and doses that are toxic. Many of the adverse events associated with colchicine are dose-related.

5. Are there approved drug products containing colchicine?

The approved versions of colchicine are tablets that also contain the active ingredient probenecid. There are two such approved products: Col-Probenecid from Watson Laboratories, and Probenecid and Colchicine from Ivax Pharmaceuticals. There are no approved products that contain only colchicine as an active ingredient. FDA is not taking any orally administered colchicine products off the market at this time, whether approved or unapproved.

6. Why is the FDA taking the injectable form of colchicine off the market at this time but not the oral forms?

There is an increased likelihood of colchicine toxicity when the drug is administered intravenously. For oral dosing in the treatment of acute gout, the dose is usually titrated by administering the drug over time until symptoms resolve or the patient begins to experience side effects, which are typically gastrointestinal. This emergence of side effects when the drug is taken orally provides a margin of safety that often prevents serious and fatal overdoses. In the case of intravenous administration, side effects are generally not experienced until the patient has already received toxic levels of colchicine. Therefore, extreme care must be exercised when colchicine is administered by this route.

FDA is not taking action at this time against those colchicine tablets that are marketed without FDA approval because the risks are less acute for colchicine tablets than they are for injectable colchicine. Like all other unapproved drugs, colchicine tablets that are marketed without FDA approval could be subject to FDA enforcement at any time. Accordingly, FDA strongly encourages the manufacturers of those products to pursue FDA approval.

7. Why does FDA caution against using intravenous colchicine to treat back pain?

In recent years, intravenous colchicine has gained popularity within the alternative medicine community as a treatment for back pain. FDA has not approved colchicine in any dosage form for this indication. Because of the toxicity of colchicine, the potential for serious adverse events and the availability of safer therapies for the treatment of back pain, FDA believes that the safety risks associated with injectable colchicine outweigh any potential benefit in using the drug for back pain. As a matter of policy, FDA does not ordinarily interfere with the practice of medicine. In the exercise of their professional judgment, physicians may generally prescribe approved drugs for unapproved uses. These warnings regarding colchicine do not change that policy.

8. Why does FDA caution against compounding colchicine for injection products and using compounded colchicine for injection?

In addition to being manufactured by pharmaceutical companies, injectable colchicine products are sometimes formulated by compounding pharmacies. There are serious risks associated with the compounding of injectable colchicine products because there is a limited margin of safety due to the narrow therapeutic index and serious toxicities associated with colchicine. Any concentration errors that occur within the course of compounding injectable colchicine can have potentially serious and fatal consequences. FDA is aware of a number of deaths attributed to improperly compounded injectable colchicine products and discourages the compounding of these products due to the serious safety risks.

9. Does FDA want to prevent pharmacy compounding?

No. FDA believes that pharmacists engaging in traditional compounding provide a valuable medical service that is important to patient health. FDA has no interest in ending traditional pharmacy compounding. FDA regards traditional pharmacy compounding as the combining or altering of ingredients by a pharmacist, in response to a licensed practitioner's prescription, to produce a drug tailored to an individual patient's special medical needs. In its simplest form, traditional compounding may involve reformulating a drug, for example, by removing a dye or preservative in response to a patient allergy. Instead, FDA focuses on the subset of inappropriate compounding described in FDA's Pharmacy Compounding CPG. The CPG is available on FDA's pharmacy compounding web page[1].

Links on this page:

1. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm

TAB 35

Guidance for FDA Staff and Industry

Marketed Unapproved Drugs — Compliance Policy Guide

Sec. 440.100
Marketed New Drugs Without Approved NDAs or ANDAs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 2006

Compliance

Guidance for FDA Staff and Industry

Marketed Unapproved Drugs — Compliance Policy Guide

Sec. 440.100
Marketed New Drugs Without Approved NDAs or ANDAs

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Rockville, MD 20857
(Phone 301-827-4573)
Internet: http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 2006

Compliance

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for FDA Staff and Industry[1]

Marketed Unapproved Drugs — Compliance Policy Guide
Chapter - 4
Subchapter - 440

Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This compliance policy guide (CPG) describes how we intend to exercise our enforcement discretion with regard to drugs marketed in the United States that do not have required FDA approval for marketing. This CPG supersedes section 440.100, Marketed New Drugs Without Approved NDAs or ANDAs (CPG 7132c.02). It applies to any drug required to have FDA approval for marketing, including new drugs covered by the Over-the-Counter (OTC) Drug Review, except for licensed biologics and veterinary drugs.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Reason for This Guidance

For historical reasons, some drugs are available in the United States that lack required FDA approval for marketing. A brief, informal summary description of the various categories of these drugs and their regulatory status is provided in Appendix A as general background for this document. The manufacturers of these drugs have not received FDA approval to legally market

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

their drugs, nor are the drugs being marketed in accordance with the OTC drug review. The new drug approval and OTC drug monograph processes play an essential role in ensuring that all drugs are both safe and effective for their intended uses. Manufacturers of drugs that lack required approval, including those that are not marketed in accordance with an OTC drug monograph, have not provided FDA with evidence demonstrating that their products are safe and effective, and so we have an interest in taking steps to either encourage the manufacturers of these products to obtain the required evidence and comply with the approval provisions of the Federal Food, Drug, and Cosmetic Act (the Act) or remove the products from the market. We want to achieve these goals without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market.

The goals of this guidance are to (1) clarify for FDA personnel and the regulated industry how we intend to exercise our enforcement discretion regarding unapproved drugs and (2) emphasize that illegally marketed drugs must obtain FDA approval.

B. Historical Enforcement Approach

FDA estimates that, in the United States today, perhaps as many as several thousand drug products are marketed illegally without required FDA approval.[2] Because we do not have complete data on illegally marketed products, and because the universe of such products is constantly changing as products enter and leave the market, we first have to identify illegally marketed products before we can contemplate enforcement action. Once an illegally marketed product is identified, taking enforcement action against the product would typically involve one or more of the following: requesting voluntary compliance; providing notice of action in a *Federal Register* notice; issuing an untitled letter; issuing a Warning Letter; or initiating a seizure, injunction, or other proceeding. Each of these actions is time-consuming and resource intensive. Recognizing that we are unable to take action immediately against all of these illegally marketed products and that we need to make the best use of scarce Agency resources, we have had to prioritize our enforcement efforts and exercise enforcement discretion with regard to products that remain on the market.

In general, in recent years, FDA has employed a risk-based enforcement approach with respect to marketed unapproved drugs. This approach includes efforts to identify illegally marketed drugs, prioritization of those drugs according to potential public health concerns or other impacts on the public health, and subsequent regulatory follow-up. Some of the specific actions the Agency has taken have been precipitated by evidence of safety or effectiveness problems that has either come to our attention during inspections or been brought to our attention by outside sources.

III. FDA'S ENFORCEMENT POLICY

In the discussion that follows, we intend to clarify our approach to prioritizing our enforcement actions and exercising our enforcement discretion with regard to the universe of unapproved, illegally marketed drug products in all categories.

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[2] This rough estimate comprises several hundred drugs (different active ingredients) in various strengths, combinations, and dosage forms from multiple distributors and repackagers.

A. Enforcement Priorities

Consistent with our risk-based approach to the regulation of pharmaceuticals, FDA intends to continue its current policy of giving higher priority to enforcement actions involving unapproved drug products in the following categories:

Drugs with potential safety risks. Removing potentially unsafe drugs protects the public from direct and indirect health threats.

Drugs that lack evidence of effectiveness. Removing ineffective drugs protects the public from using these products in lieu of effective treatments. Depending on the indication, some ineffective products would, of course, pose safety risks as well.

Health fraud drugs. FDA defines health fraud as "[t]he deceptive promotion, advertisement, distribution or sale of articles . . . that are represented as being effective to diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a beneficial effect on health, but which have not been scientifically proven safe and effective for such purposes. Such practices may be deliberate or done without adequate knowledge or understanding of the article" (CPG Sec. 120.500). Of highest priority in this area are drugs that present a direct risk to health. Indirect health hazards exist if, as a result of reliance on the product, the consumer is likely to delay or discontinue appropriate medical treatment. Indirect health hazards will be evaluated for enforcement action based on section 120.500, Health Fraud - Factors in Considering Regulatory Action (CPG 7150.10). FDA's health fraud CPG outlines priorities for evaluating regulatory actions against indirect health hazard products, such as whether the therapeutic claims are significant, whether there are any scientific data to support the safety and effectiveness of the product, and the degree of vulnerability of the prospective user group (CPG Sec. 120.500).

Drugs that present direct challenges to the new drug approval and OTC drug monograph systems. The drug approval and OTC drug monograph systems are designed to avoid the risks associated with potentially unsafe, ineffective, and fraudulent drugs. The drugs described in the preceding three categories present direct challenges to these systems, as do unapproved drugs that directly compete with an approved drug, such as when a company obtains approval of a new drug application (NDA) for a product that other companies are marketing without approval (*see* section III.C., Special Circumstances – Newly Approved Product). Also included are drugs marketed in violation of a final and effective OTC drug monograph. Targeting drugs that challenge the drug approval or OTC drug monograph systems buttresses the integrity of these systems and makes it more likely that firms will comply with the new drug approval and monograph requirements, which benefits the public health.

Unapproved new drugs that are also violative of the Act in other ways. The Agency also intends, in circumstances that it considers appropriate, to continue its policy of enforcing the preapproval requirements of the Act against a drug or firm that also violates another provision of the Act, even if there are other unapproved versions of the drug

made by other firms on the market. For instance, if a firm that sells an unapproved new drug also violates current good manufacturing practice (CGMP) regulations, the Agency is not inclined to limit an enforcement action in that instance to the CGMP violations. Rather, the Agency may initiate a regulatory action that targets both the CGMP violation *and* the violation of section 505 of the Act (21 U.S.C. 355). This policy efficiently preserves scarce Agency resources by allowing the Agency to pursue all applicable charges against a drug and/or a firm and avoiding duplicative action. *See United States v. Sage Pharmaceuticals, Inc.*, 210 F.3d 475, 479-80 (5th Cir. 2000).

Drugs that are reformulated to evade an FDA enforcement action. The Agency is also aware of instances in which companies that anticipate an FDA enforcement action against a specific type or formulation of an unapproved product have made formulation changes to evade that action, but have not brought the product into compliance with the law. Companies should be aware that the Agency is not inclined to exercise its enforcement discretion with regard to such products. Factors that the Agency may consider in determining whether to bring action against the reformulated products include, but are not limited to, the timing of the change, the addition of an ingredient without adequate scientific justification (*see, e.g.*, 21 CFR 300.50 and 330.10(a)(4)(iv)), the creation of a new combination that has not previously been marketed, and the claims made for the new product.

B. Notice of Enforcement Action and Continued Marketing of Unapproved Drugs

FDA is not required to, and generally does not intend to, give special notice that a drug product may be subject to enforcement action, unless FDA determines that notice is necessary or appropriate to protect the public health.[3] The issuance of this guidance is intended to provide notice that any product that is being marketed illegally is subject to FDA enforcement action at any time.[4] The only exception to this policy is, as set forth elsewhere, that generally products subject to an ongoing DESI[5] proceeding or ongoing OTC drug monograph proceeding (i.e., an OTC product that is part of the OTC drug review for which an effective final monograph is not yet in place) may remain on the market during the pendency of

[3] For example, in 1997, FDA issued a *Federal Register* notice declaring all orally administered levothyroxine sodium products to be new drugs and requiring manufacturers to obtain approved new drug applications (62 FR 43535, August 14, 1997). Nevertheless, FDA gave manufacturers 3 years (later extended to 4 (65 FR 24488, April 26, 2000)) to obtain approved applications and allowed continued marketing without approved new drug applications because FDA found that levothyroxine sodium products were medically necessary to treat hypothyroidism and no alternative drug provided an adequate substitute.

[4] For example, FDA may take action at any time against a product that was originally marketed before 1938, but that has been changed since 1938 in such a way as to lose its *grandfather* status (21 U.S.C. 321(p)).

[5] The Drug Efficacy Study Implementation (DESI) was the process used by FDA to evaluate for effectiveness for their labeled indications over 3,400 products that were approved only for safety between 1938 and 1962. DESI is explained more fully in the appendix to this document.

that proceeding[6] and any additional period specifically provided in the proceeding (such as a delay in the effective date of a final OTC drug monograph).[7] However, once the relevant DESI or OTC drug monograph proceeding is completed and any additional grace period specifically provided in the proceeding has expired, all products that are not in compliance with the conditions for marketing determined in that proceeding are subject to enforcement action at any time without further notice (*see, e.g.*, 21 CFR 310.6).

FDA intends to evaluate on a case-by-case basis whether justification exists to exercise enforcement discretion to allow continued marketing for some period of time after FDA determines that a product is being marketed illegally. In deciding whether to allow such a grace period,[8] we may consider the following factors: (1) the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of legally marketed products to meet the needs of patients taking the drug); (2) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application; (3) the burden on affected parties of immediately removing the products from the market; (4) the Agency's available enforcement resources; and (5) any special circumstances relevant to the particular case under consideration.

C. Special Circumstances — Newly Approved Product

Sometimes, a company may obtain approval of an NDA for a product that other companies are marketing without approval.[9] We want to encourage this type of voluntary compliance with the new drug requirements because it benefits the public health by increasing the assurance that marketed drug products are safe and effective — it also reduces the resources that FDA must expend on enforcement. Thus, because they present a direct challenge to the drug approval system, FDA is more likely to take enforcement action against remaining unapproved drugs in this kind of situation. However, we intend to take into account the circumstances once the product is approved in determining how to exercise our enforcement discretion with regard to the unapproved products. In exercising enforcement discretion, we intend to balance the need to provide incentives for voluntary compliance against the implications of enforcement actions on the marketplace and on consumers who are accustomed to using the marketed products.

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[6] OTC drugs covered by ongoing OTC drug monograph proceedings may remain on the market as provided in current enforcement policies. *See, e.g.*, CPG sections 450.200 and 450.300 and 21 CFR part 330. This document does not affect the current enforcement policies for such drugs.

[7] Sometimes, a final OTC drug monograph may have a delayed effective date or provide for a specific period of time for marketed drugs to come into compliance with the monograph. At the end of that period, drugs that are not marketed in accordance with the monograph are subject to enforcement action and the exercise of enforcement discretion in the same way as any other drug discussed in this CPG.

[8] For purposes of this guidance, the terms *grace period* and *allow a grace period* refer to an exercise of enforcement discretion by the Agency (i.e., a period of time during which FDA, as a matter of discretion, elects not to initiate a regulatory action on the ground that an article is an unapproved new drug).

[9] These may be products that are the same as the approved product or somewhat different, such as products of different strength.

When a company obtains approval to market a product that other companies are marketing without approval, FDA normally intends to allow a grace period of roughly 1 year from the date of approval of the product before it will initiate enforcement action (e.g., seizure or injunction) against marketed unapproved products of the same type. However, the grace period provided is expected to vary from this baseline based upon the following factors: (1) the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of the holder of the approved application to meet the needs of patients taking the drug); (2) whether the effort to obtain approval was publicly disclosed;[10] (3) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application; (4) the burden on affected parties of removing the products from the market; (5) the Agency's available enforcement resources; and (6) any other special circumstances relevant to the particular case under consideration. To assist in an orderly transition to the approved product(s), in implementing a grace period, FDA may identify interim dates by which firms should first cease *manufacturing* unapproved forms of the drug product, and later cease *distributing* the unapproved product.

The length of any grace period and the nature of any enforcement action taken by FDA will be decided on a case-by-case basis. Companies should be aware that a Warning Letter may not be sent before initiation of enforcement action and should not expect any grace period that is granted to protect them from the need to leave the market for some period of time while obtaining approval. Companies marketing unapproved new drugs should also recognize that, while FDA normally intends to allow a grace period of roughly 1 year from the date of approval of an unapproved product before it will initiate enforcement action (e.g., seizure or injunction) against others who are marketing that unapproved product, it is possible that a substantially shorter grace period would be provided, depending on the individual facts and circumstances.[11]

The shorter the grace period, the more likely it is that the first company to obtain an approval will have a period of de facto market exclusivity before other products obtain approval. For example, if FDA provides a 1-year grace period before it takes action to remove unapproved competitors from the market, and it takes 2 years for a second application to be approved, the first approved product could have 1 year of market exclusivity before the onset of competition. If FDA provides for a shorter grace period, the period of effective exclusivity could be longer.

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[10] For example, at the Agency's discretion, we may provide for a shorter grace period if an applicant seeking approval of a product that other companies are marketing without approval agrees to publication, around the time it submits the approval application, of a *Federal Register* notice informing the public that the applicant has submitted that application. A shortened grace period may also be warranted if the fact of the application is widely known publicly because of applicant press releases or other public statements. Such a grace period may run from the time of approval or from the time the applicant has made the public aware of the submission, as the Agency deems appropriate.

[11] Firms are reminded that this CPG does not create any right to a grace period; the length of the grace period, if any, is solely at the discretion of the Agency. For instance, firms should not expect any grace period when the public health requires immediate removal of a product from the market, or when the Agency has given specific prior notice in the *Federal Register* or otherwise that a drug product requires FDA approval.

FDA hopes that this period of market exclusivity will provide an incentive to firms to be the first to obtain approval to market a previously unapproved drug.[12]

D. Regulatory Action Guidance

District offices are encouraged to refer to CDER for review (with copies of labeling) any unapproved drugs that appear to fall within the enforcement priorities in section III.A. Charges that may be brought against unapproved drugs include, but are not limited to, violations of 21 U.S.C. 355(a) and 352(f)(1) of the Act. Other charges may also apply based on, among others, violations of 21 U.S.C. 351(a)(2)(B) (CGMP), 352(a) (misbranding), or 352(o) (failure to register or list).

[12] The Agency understands that, under the Act, holders of NDAs must list patents claiming the approved drug product and that newly approved drug products may, in certain circumstances, be eligible for marketing exclusivity. Listed patents and marketing exclusivity may delay the approval of competitor products. If FDA believes that an NDA holder is manipulating these statutory protections to inappropriately delay competition, the Agency will provide relevant information on the matter to the Federal Trade Commission (FTC). In the past, FDA has provided information to the FTC regarding patent infringement lawsuits related to pending abbreviated new drug applications (ANDAs), citizen petitions, and scientific challenges to the approval of competitor drug products.

APPENDIX

BRIEF HISTORY OF FDA MARKETING APPROVAL REQUIREMENTS AND CATEGORIES OF DRUGS THAT LACK REQUIRED FDA APPROVAL[13]

Key events in the history of FDA's drug approval regulation and the categories of drugs affected by these events are described below.

A. 1938 and 1962 Legislation

The original Federal Food and Drugs Act of June 30, 1906, first brought drug regulation under federal law. That Act prohibited the sale of adulterated or misbranded drugs, but did not require that drugs be approved by FDA. In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act (the Act), which required that new drugs be approved for safety. As discussed below, the active ingredients of many drugs currently on the market were first introduced, at least in some form, before 1938. Between 1938 and 1962, if a drug obtained approval, FDA considered drugs that were identical, related, or similar (IRS) to the approved drug to be covered by that approval, and allowed those IRS drugs to be marketed without independent approval. Many manufacturers also introduced drugs onto the market between 1938 and 1962 based on their own conclusion that the products were generally recognized as safe (GRAS) or based on an opinion from FDA that the products were not new drugs. Between 1938 and 1962, the Agency issued many such opinions, although all were formally revoked in 1968 (*see* 21 CFR 310.100).

B. DESI

In 1962, Congress amended the Act to require that a *new drug* also be proven effective, as well as safe, to obtain FDA approval. This amendment also required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that FDA had approved as *safe* between 1938 and 1962 through the new drug approval process.

FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. The NAS/NRC created 30 panels of 6 professionals each to conduct the review, which was broken down into specific drug categories. The NAS/NRC reports for these drug products were submitted to FDA in the late 1960s and early 1970s. The Agency reviewed and re-evaluated the findings of each panel and published its findings in *Federal Register* notices. FDA's administrative implementation of the NAS/NRC reports was called the Drug Efficacy Study Implementation (DESI). DESI covered the 3,400 products specifically reviewed by the NAS/NRCs as well as the even larger number of IRS products that entered the market without FDA approval.

Because DESI products were covered by approved (pre-1962) applications, the Agency concluded that, prior to removing products not found effective from the market, it would follow

[13] This brief history document should be viewed as a secondary source. To determine the regulatory status of a particular drug or category of drugs, the original source documents cited should be consulted.

procedures in the Act and regulations that apply when an approved new drug application is withdrawn:

- All initial DESI determinations are published in the *Federal Register* and, if the drug is found to be less than fully effective, there is an opportunity for a hearing.
- The Agency considers the basis of any hearing request and either grants the hearing or denies the hearing on summary judgment and publishes its final determination in the *Federal Register*.
- If FDA's final determination classifies the drug as effective for its labeled indications, as required by the Act, FDA still requires approved applications for continued marketing of the drug and all drugs IRS to it – NDA supplements for those drugs with NDAs approved for safety, or new ANDAs or NDAs, as appropriate, for IRS drugs. DESI-effective drugs that do not obtain approval of the required supplement, ANDA, or NDA are subject to enforcement action.
- If FDA's final determination classifies the drug as ineffective, the drug and those IRS to it can no longer be marketed and are subject to enforcement action.

1. Products Subject to Ongoing DESI Proceedings

Some unapproved marketed products are undergoing DESI reviews in which a final determination regarding efficacy has not yet been made. In addition to the products specifically reviewed by the NAS/NRC (i.e., those products approved for safety only between 1938 and 1962), this group includes unapproved products identical, related, or similar to those products specifically reviewed (*see* 21 CFR 310.6). In virtually all these proceedings, FDA has made an initial determination that the products lack substantial evidence of effectiveness, and the manufacturers have requested a hearing on that finding. It is the Agency's longstanding policy that products subject to an ongoing DESI proceeding may remain on the market during the pendency of the proceeding. *See, e.g., Upjohn Co. v. Finch*, 303 F. Supp. 241, 256-61 (W.D. Mich. 1969).[14]

2. Products Subject to Completed DESI Proceedings

Some unapproved marketed products are subject to already-completed DESI proceedings and lack required approved applications. This includes a number of products IRS to DESI products for which approval was withdrawn due to a lack of substantial evidence of effectiveness. This group also includes a number of products IRS to those DESI products for which FDA made a

[14] Products first marketed after a hearing notice is issued with a different formulation than those covered by the notice are not considered subject to the DESI proceeding. Rather, they need approval prior to marketing. Under longstanding Agency policies, a firm holding an NDA on a product for which a DESI hearing is pending must submit a supplement prior to reformulating that product. The changed formulation may not be marketed as a related product under the pending DESI proceeding; it is a new drug, and it must be approved for safety and efficacy before it can be legally marketed. *See, e.g.*, "Prescription Drugs Offered for Relief of Symptoms of Cough, Cold, or Allergy" (DESI 6514), 49 FR 153 (January 3, 1984) (Dimetane and Actifed); "Certain Drugs Containing Antibiotic, Corticosteroid, and Antifungal Components" (DESI 10826), 50 FR 15227 (April 17, 1985) (Mycolog). *See also* 21 U.S.C. 356a(c)(2)(A). Similarly, firms without NDAs cannot market new formulations of a drug without first getting approval of an NDA.

final determination that the product is effective, but applications for the IRS products have not been both submitted and approved as required under the statute and longstanding enforcement policy (*see* 21 CFR 310.6). FDA considers all products described in this paragraph to be marketed illegally.

C. Prescription Drug Wrap-Up

As mentioned above, many drugs came onto the market before 1962 without FDA approvals. Of these, many claimed to have been marketed prior to 1938 or to be IRS to such a drug. Drugs that did not have pre-1962 approvals and were not IRS to drugs with pre-1962 approvals were not subject to DESI. For a period of time, FDA did not take action against these drugs and did not take action against new unapproved drugs that were IRS to these pre-1962 drugs that entered the market without approval.

Beginning in 1983, it was discovered that one drug that was IRS to a pre-1962 drug, a high potency Vitamin E intravenous injection named E-Ferol, was associated with adverse reactions in about 100 premature infants, 40 of whom died. In November of 1984, in response to this, a congressional oversight committee issued a report to FDA expressing the committee's concern regarding the thousands of unapproved drug products in the marketplace.

In response to the E-Ferol tragedy, CDER assessed the number of pre-1962 non-DESI marketed drug products. To address those drug products, the Agency significantly revised and expanded CPG section 440.100 to cover all marketed unapproved prescription drugs, not just DESI products. The program for addressing these marketed unapproved drugs and certain others like them became known as the *Prescription Drug Wrap-Up*. Most of the Prescription Drug Wrap-Up drugs first entered the market before 1938, at least in some form. For the most part, the Agency had evaluated neither the safety nor the effectiveness of the drugs in the Prescription Drug Wrap-Up.

A drug that was subject to the Prescription Drug Wrap-Up is marketed illegally, unless the manufacturer of such a drug can establish that its drug is grandfathered or otherwise not a *new drug*.

Under the 1938 grandfather clause (*see* 21 U.S.C. 321(p)(1)), a drug product that was on the market prior to passage of the 1938 Act and which contained in its labeling the same representations concerning the conditions of use as it did prior to passage of that Act was not considered a *new drug* and therefore was exempt from the requirement of having an approved new drug application.

Under the 1962 grandfather clause, the Act exempts a drug from the effectiveness requirements if its composition and labeling has not changed since 1962 and if, on the day before the 1962 Amendments became effective, it was (a) used or sold commercially in the United States, (b) not a new drug as defined by the Act at that time, and (c) not covered by an effective application. *See* Pub. L. 87-781, section 107 (reprinted following 21 U.S.C.A. 321); *see also USV Pharmaceutical Corp. v. Weinberger,* 412 U.S. 655, 662-66 (1973).

The two grandfather clauses in the Act have been construed very narrowly by the courts. FDA believes that there are very few drugs on the market that are actually entitled to grandfather status because the drugs currently on the market likely differ from the previous versions in some respect, such as formulation, dosage or strength, dosage form, route of administration, indications, or intended patient population. If a firm claims that its product is grandfathered, it is that firm's burden to prove that assertion. *See* 21 CFR 314.200(e)(5); *see also United States v. An Article of Drug (Bentex Ulcerine),* 469 F.2d 875, 878 (5th Cir. 1972); *United States v. Articles of Drug Consisting of the Following: 5,906 Boxes*, 745 F.2d 105, 113 (1st Cir 1984).

Finally, a product would not be considered a *new drug* if it is generally recognized as safe and effective (GRAS/GRAE) and has been used to a material extent and for a material time. *See* 21 U.S.C. 321(p)(1) and (2). As with the grandfather clauses, this has been construed very narrowly by the courts. *See, e.g., Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); *United States v. 50 Boxes More or Less Etc.*, 909 F.2d 24, 27-28 (1st Cir. 1990); *United States v. 225 Cartons . . . Fiorinal*, 871 F.2d 409 (3rd Cir. 1989). *See also* Letter from Dennis E. Baker, Associate Commissioner for Regulatory Affairs, FDA, to Gary D. Dolch, Melvin Spigelman, and Jeffrey A. Staffa, Knoll Pharmaceutical Co. (April 26, 2001) (on file in FDA Docket No. 97N-0314/CP2) (finding that Synthroid, a levothyroxine sodium product, was not GRAS/GRAE).

As mentioned above, the Agency believes it is not likely that any currently marketed prescription drug product is grandfathered or is otherwise not a *new drug*. However, the Agency recognizes that it is at least theoretically possible. No part of this guidance, including the Appendix, is a finding as to the legal status of any particular drug product. In light of the strict standards governing exceptions to the approval process, it would be prudent for firms marketing unapproved products to carefully assess whether their products meet these standards.

D. New Unapproved Drugs

Some unapproved drugs were first marketed (or changed) after 1962. These drugs are on the market illegally. Some also may have already been the subject of a formal Agency finding that they are new drugs. *See, e.g.*, 21 CFR 310.502 (discussing, among other things, controlled/timed release dosage forms).

E. Over-the-Counter (OTC) Drug Review

Although OTC drugs were originally included in DESI, FDA eventually concluded that this was not an efficient use of resources. The Agency also was faced with resource challenges because it was receiving many applications for different OTC drugs for the same indications. Therefore, in 1972, the Agency implemented a process of reviewing OTC drugs through rulemaking by therapeutic classes (e.g., antacids, antiperspirants, cold remedies). This process involves convening an advisory panel for each therapeutic class to review data relating to claims and active ingredients. These panel reports are then published in the *Federal Register*, and after FDA review, tentative final monographs for the classes of drugs are published. The final step is the publication of a final monograph for each class, which sets forth the allowable claims, labeling, and active ingredients for OTC drugs in each class (*see, e.g.*, 21 CFR part 333). Drugs marketed in accordance with a final monograph are considered to be generally recognized as safe and effective (GRAS/GRAE) and do not require FDA approval of a marketing application.

Final monographs have been published for the majority of OTC drugs. Tentative final monographs are in place for virtually all categories of OTC drugs. FDA has also finalized a number of *negative monographs* that list therapeutic categories (*e.g.*, OTC daytime sedatives, 21 CFR 310.519) in which no OTC drugs can be marketed without approval. Finally, the Agency has promulgated a list of active ingredients that cannot be used in OTC drugs without approved applications because there are inadequate data to establish that they are GRAS/GRAE (*e.g.*, phenolphthalein in stimulant laxative products, 21 CFR 310.545(a)(12)(iv)(B)).

OTC drugs covered by ongoing OTC drug monograph proceedings may remain on the market as provided in current enforcement policies (*see, e.g.*, CPG sections 450.200 and 450.300, and 21 CFR part 330). This document does not affect the current enforcement policies for such drugs.

OTC drugs that need approval, either because their ingredients or claims are not within the scope of the OTC drug review or because they are not allowed under a final monograph or another final rule, are illegally marketed. For example, this group would include a product containing an ingredient determined to be ineffective for a particular indication or one that exceeds the dosage limit established in the monograph. Such products are new drugs that must be approved by FDA to be legally marketed.

TAB 36

REDACTED

MUTUAL_001020399
through
MUTUAL_001020403

TAB 37

REDACTED

TAB 38

REDACTED

MUTUAL_000868238
through
MUTUAL_000868241

TAB 39

REDACTED

TAB 40

REDACTED

TAB 41

REDACTED

TAB 42

REDACTED

EXHIBIT 43

Inspections, Compliance, Enforcement, and Criminal Investigations

Sunrise Pharmaceutical, Inc. 1/14/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054
Telephone (973) 331-4910

January 14, 2010

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Utpal Patel
Chief Executive Officer
Sunrise Pharmaceutical, Inc.
665 E. Lincoln Avenue
Rahway, New Jersey 07065

10-NWJ-03

Dear Mr. Patel:

This is regarding our June 19 through July 17, 2009 inspection of your pharmaceutical manufacturing facility, Sunrise Pharmaceutical, Inc., located at 665 E. Lincoln Avenue, Rahway, New Jersey. The inspection identified significant violations of the Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. These violations cause your drug products to be adulterated within the meaning of section 501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 351 (a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with CGMP regulations.

In addition, you manufacture a number of prescription drugs without approved applications. As described below, these drugs are unapproved new drugs, and by introducing them into interstate commerce you are in violation of 21 U.S.C. 355(a) (section 505(a) of the Act). These drugs are also misbranded under 21 U.S.C. 352(f)(1) (section 502(f)(1) of the Act).

We have reviewed your firm's responses of July 27, September 17, and November 18, 2009, and note that they lack sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

CGMP Violations

1. Your firm has not established laboratory control mechanisms, including any change, and has failed to document quality control unit review and approval at the time of performance [21 CFR 211.160(a)]. For example,

   a. Out-of-specification (OOS) humidity levels for the controlled room temperature stability chamber were noted on January 27, March 17, and April 5 and 6, 2009. Investigations and corrective actions were not conducted at the time to address these out-of-specification results. During the inspection, however, the Quality Unit presented back-dated service requests to investigators as evidence of proper OOS result handling when in fact, no actual service requests were initiated.

   b. Investigation report #05072009 dated May 7, 2009, was initiated following a power failure during the coating of Senna & Docusate Sodium Film Coated Tablets, 8.6mg/50mg, lot 0904004. According to the report, the lot was inspected for peeled film tablets during May 8-26, 2009; however, the corrective actions and disposition of drug product were approved by the Quality Unit on May 7, 2009.

Regarding the above examples, the corrective action in your July 27, 2009 response states, "The employees involved will be retrained and warned that a future recurrence will have zero tolerance resulting in severe action, including possible immediate termination." Your response fails to describe the specific type of training that will be provided and how the effectiveness of the training will be evaluated.

This is a repeat observation from the February and August 2007 inspections.

2. Your firm does not have adequate written procedures for production and process control designed to assure that your drug products have the identity, strength, quality, and purity that they purport or are represented to possess [21 CFR 211.100(a)].

For example, the validation studies for Guaifenesin and Dextromethorphan HBr 400mg/20mg Caplets are inadequate in that they do not demonstrate that the manufacturing process is reproducible. Specifically, one of your three validation lots, S0712012 (manufactured December 21, 2007), failed the blend uniformity test specifications. This same lot was blended for an additional 10 minutes without the review and approval of the Quality Unit. In addition, the validation protocol was not approved until April 2008, which is four months after the validation lot SO712012 was manufactured.

In your July 27, 2009 response, you promised to retrain your employees. However, we are concerned that this same commitment was made in the past for other deficiencies. Please specify the type of training that will be offered and how retraining will prevent recurrence of violations.

In your September 17, 2009 response, you provided an amendment to the validation report which referenced an additional validation lot (S0908003) of Guaifenesin and Dextromethorphan HBr 400mg/20mg Caplets. This additional lot was manufactured to fulfill your protocol requirements. However, your response does not specifically address: a) the blend uniformity failure for validation lot S0712012; b) whether the mixing time is a critical process parameter; and c) your rationale for concluding that your process is validated. You have not demonstrated that

your manufacturing process is in a sufficient state of control and capable of reproducing acceptable product.

In addition, Section 5.4.2, Sampling Requirements, in your Process Validation Protocol, PVP-2000M-122T-04, states that **(b)(4)** tablets should be collected at **(b)(4)** for analytical testing. However, 10 tablets were collected from 14 sampling locations for a total of 140 tablets in lot S0908003. Your response does not address this apparent deviation from your protocol. Also, be advised that the degree of validation sampling (e.g.,number and frequency) and testing should be more extensive (than routine production) in order to provide sufficient statistical confidence of quality within a batch and between batches. Please address your confidence level when sampling a total of 140 tablets from a lot of **(b)(4)** tablets (protocol batch size).

Your response also fails to address the additional mixing of validation lot S0712012. We reviewed the amendment to your Process Validation Report, dated June 23, 2009, regarding the 10 additional minutes of mixing time (for a total **(b)(4)** of minutes). Your amendment states that "All Lots tested were complying with tolerance's set." However, your amendment further states that your total mixing time (i.e., established tolerance) was **(b)(4)** minutes as per your batch records and that the "Additional 10 minutes time has no impact on product Quality." Please provide the total mixing time established in the validation protocol and specifically, address any deviation from this established specification during the manufacture of the validation lot S0712012. Also, provide your rationale for concluding that your validation data supports an additional 10 minutes of mixing time.

In addition, periodic process verification is essential for ensuring that a manufacturing process continues to be reproducible.

3. Your firm does not have master production and control records that justify variation in the amount of components necessary for the preparation of the dosage form [21 CFR 211.186(b)(4)].

For example, some of your products were formulated with excess amounts of active pharmaceutical ingredient (API). Specific instances include an excess of Dextromethophorphan HBr API in Guaifenesin and Dextromethorphan HBr Tablets, a excess of Colchicine API in Colchicine Tablets, and an excess of Hyoscyamine Sulfate API in Hyoscyamine Sulfate Subligual Tablets. You failed to provide documented scientific justification to explain why the excess API is necessary. In addition, you deemed the excess amounts as necessary due to "process loss;" however, none of these losses were documented.

Your July 27,2009 response states 'The master formulas justify whenever overages are used, i.e., moisture or solvent compensation." This response is inadequate because it does not address why excess amounts of API are needed for moisture or solvent compensation, or manufacturing process losses when charging the APIs used in drug product manufacturing. Your process is not considered to be in an adequate state of control when excess API (than as required in your batch records) is routinely used by your firm. To ensure proper formulation, you must document and justify the need for any excess amount of a component in each batch record.

4. Your firm has not established an adequate written testing program designed to assess the stability characteristics of your drug products in determining appropriate storage conditions and expiration dates since your program does not include reliable, meaningful, and specific test methods [21 CFR 211.166(a)(3)].

Specifically, some of your firm's analytical methods have not been validated to demonstrate that they are stability indicating. In other instances, test methods that you claim to be stability indicating are inadequate or not followed by your firm. For example,

a. A stability indicating test method has not been developed and validated for Senna & Docusate Sodium tablets.

b. Stability indicating test methods are developed, but not validated, for Guaifenesin and Dextromethorphan HBr Tablets, and impurity specifications have not been established for the finished product release or stability samples. as required by 21 CFR 211.160(b).

c. Validated stability indicating test methods are established, but are not followed, to analyze impurity levels for Phenazopyradine HCI Tablets, Bisacodyl Tablets, and **(b)(4)**. Further, impurity specifications have not been established for any of the aforementioned finished product release testing or stability samples as required by 21 CFR 211.160(b).

Your September 17, 2009 response did not include the following: a) specifications; b) allowable levels of impurities; or c) test results regarding impurity testing for Bisacodyl tablets. We note your response states that your firm has discontinued manufacturing of **(b)(4)** and Phenazopyradine HCI Tablets.

Your November 18, 2009 response included method validation impurity testing results for Senna & Docusate Sodium Tablets and the Guaifenesin & Dextromethorphan drug products. However, your response did not state whether the impurity specification of Not More Than (NMT) **(b)(4)** noted in the method validation report, will be used during routine testing or stability testing in the future.

5. Your firm has not followed the written procedures for reprocessing batches that do not conform to standards or specifications for ensuring that the reprocessed batches conform with all established standards, specifications, and characteristics [21 CFR 211.115(a)].

For example, your firm did not follow SOP SMP-07, "Performance, Documentation and Approval of Reprocessing Operation," after Guaifenesin and Dextromethorphan HBr Caplets, validation lot S0712012, failed blend uniformity testing. A reprocessing master batch record was not prepared to reprocess the batch as per your SOP. Instead, production personnel remixed and resampled the lot, after which passing results were obtained and the lot was released.

The corrective action in your July 27, 2009 response indicates that employees will be retrained on existing procedures. This response is inadequate because it fails to describe when and how the employees will be retrained.

6. Your firm has not exercised appropriate controls over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel [21 CFR 211.68(b)].

For example, your firm lacks systems to ensure that all electronic data generated in your Quality Control laboratory is secure and remains unaltered. All analysts have system administrator privileges that allow them to modify, overwrite, and delete original raw data files on the **(b)(4)** used **(b)(4)** in the High Performance Liquid Chromatography (HPLC) units. There are no procedures that address the security measures in place for generation and modification of electronic data files for these instruments used for raw material, in-process, finished product and stability testing. In addition, your firm's review of laboratory data does not include a review of an audit trail or revision history to determine if unapproved changes have been made.

Your September 17, 2009 response states that you replaced the **(b)(4)** HPLC systems operating on **(b)(4)** software with **(b)(4)** new qualified HPLC units from **(b)(4)** software. This validation information will be reviewed at the next inspection. In addition, your response is inadequate because it lacks a retrospective evaluation of the data from the former HPLC units. This will prevent an alteration of data prior to implementation of your corrective actions. Further, your response does not address security procedures to ensure that the data generated using the new HPLC units is secure and remains unaltered.

This is a repeat observation from the February and August 2007 inspections.

Misbranded and Unapproved New Drugs

New drug and misbranding violations for prescription drug products

In addition to the CGMP violations, you manufacture and market unapproved new drugs in violation of the Act at your facility at your facility at 665 E. Lincoln Avenue in Rahway, New Jersey. Based on the information collected during the inspection, you manufacture the following prescription drugs, including but not limited to:

- Colchicine Tablets, 0.6 mg

- Hyoscyamine Sulfate Tablets, USP, 0.125 mg
- Hyoscyamine Sulfate Orally Disintegrating Tablets, 0.125 mg
- Hyoscyamine Sulfate Sublingual Tablets, 0.125 mg

The above products are drugs within the meaning of Section 201 (g) of the Act, [21 U.S.C. 321 (g)] because as demonstrated by their labeling, they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases. Further, they are "new drugs" within the meaning of Section 201 (p) of the Act [21 U.S.C. 321 (p)] because they are not generally recognized as safe and effective for their labeled uses. Under Sections 301 (d) and 505(a) of the Act [21 U.S.C. 331 (a), (d) and 355(a)] a new drug may not be introduced into or delivered for introduction into interstate commerce unless an application approved by FDA under either section 505(b) or (j) of the Act [21 U.S.C. 355(b) or (j)] is in effect for the drug. Based on our information, there are no FDA-approved applications on file for these drug products.

Additionally, the above products are misbranded because, as prescription drugs, adequate directions cannot be written for them so that a layman can use these products safely for their intended uses. Consequently, their labeling fails to bear adequate directions for use as required under Sections 502(f)(1) of the Act [21 U.S.C. 352(f)(1)] and because the products lack required approved applications, they are not exempt from this requirement under 21 CFR 201.115. The introduction or delivery for introduction into interstate commerce of these products without approved new drug applications violates Section 301 (a) and (d) of the Act [21 U.S.C. 331 (a) and (d)].

New drug and misbranding violations for retail OTC drug products

Based on the information collected during the inspection, you manufacture and package for retail sale the following finished OTC drug products, including but not limited to:

- Sunrise Pharmaceutical, Aspirin, 325 mg, Pain Reliever Enteric Safety Coated, 100 Tablets
- Sunrise Pharmaceutical, Aspirin, 325 mg, Pain Reliever Enteric Safety Coated, 1000 Tablets
- Sunrise Pharmaceutical, Bisacodyl USP, 5 mg, Laxative, Enteric Sugar Coated, 100 Tablets
- Sunrise Pharmaceutical, Bisacodyl USP, 5 mg, Laxative, 1000 Enteric Sugar Coated Tablets
- **(b)(4)** Bisacodyl Tablets, USP, 5 mg, Delayed-Release Tablets Enteric Coated, 100 Tablets
- **(b)(4)** Bisacodyl Tablets, USP, 5 mg, Delayed-Release Tablets Enteric Coated, 1000 Tablets
- **(b)(4)** (Bisacodyl USP), Comfort Coated Stimulant Laxative, 5 mg, 100 Tablets (distributed by **(b)(4)**)
- **(b)(4)** Enteric Coated Stimulant Laxative (Bisacodyl USP), 5 mg, 100 Tablets (distributed by **(b)(4)**)
- Sunrise Pharmaceutical, Guaifenesin, 400 mg, Expectorant, 100 Tablets
- **(b)(4)** Guiafenesin, 400 mg, Expectorant, 100 Tablets (distributed by **(b)(4)**)
- Sunrise Pharmaceutical, Guaifenesin, 400 mg, Dextromethorphan HBR 20mg, Expectorant/Antitussive, 30 Tablets
- **(b)(4)**, Diphenhydramine HCL Capsules, USP, 50 mg, Antihistamine, 100 Capsules
- **(b)(4)** Diphenhydramine HCL Capsules, USP, 50 mg, Antihistamine, 1000 Capsules
- **(b)(4)** Diphenhydramine HCL Capsules, USP, 25 mg, Antihistamine, 1000 Capsules
- Sunrise Pharmaceutical, Aspirin, 81 mg, Pain Reliever Adult Low Dose, Enteric Safety Coated, 120 Tablets
- Sunrise Pharmaceutical, Aspirin, 81 mg, Pain Reliever Adult Low Dose, Enteric Safety Coated, 1000 Tablets
- Sunrise Pharmaceutical, Senna, 8.6 mg, Docusate Sodium, 50 mg, Natural Vegetable Laxative plus Stool Softener, 60 Tablets
- **(b)(4)** Natural Vegetable Laxative Plus Stool Softener, 100 Tablets
- **(b)(4)** Natural Vegetable Laxative Plus Stool Softener, 100 Tablets
- **(b)(4)** Docusate Sodium, Stool Softener Plus Laxative, 100 Tablets
- **(b)(4)** Docusate Sodium, Stool Softener Plus Laxative, 1000 Tablets

The above products are drugs within the meaning of section 201(g) of the Act, [21 U.S.C.321 (g)] because as demonstrated by their labeling, they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases.

Further, the three **(b)(4)** Diphenhydramine HCL Capsule products manufactured and packaged by Sunrise Pharmaceuticals as noted above for use as antihistamines are "new drugs" within the meaning of Section 201(p) of the Act [21 U.S.C. 321(p)] because they are not generally recognized as safe and effective for their labeled uses. Specifically, OTC drug products intended for use as OTC antihistamines with an active ingredient of diphenhydramine HCL, are subject to the requirements of the final monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC Human Use at 21 CFR Part 341. The labeling for all three diphenhydramine HCL products state the following indications for uses: "temporarily relieves· hay fever or other upper respiratory allergies like: • runny nose· sneezing ·watery eyes· itchy nose or throat". However, the final monograph does not allow for the use of antihistamines to relieve hay fever or other upper respiratory allergies, rather the permitted uses are for temporary relief of such symptoms listed on your products label (i.e. runny nose, sneezing, watery eyes, itchy nose or throat) "due to hay fever ... or other upper respiratory allergies ...."[emphasis added] (21 CFR 341.72(b)).

Therefore, the three **(b)(4)** Diphenhydramine HCL products described above are "new drugs" as defined by section 201 (p) of the Act, 21 U.S.C. 321 (p) and 21 CFR 310.3(h), because the labeled uses are not in accordance with the Antihistamine Final Monograph (21 CFR 341.72). Additionally, none of the three diphenhydramine HCL products are the subject of an approved new drug application. Because the three **(b)(4)** Diphenhydramine HCL products above are new drugs and not the subject of an approved new drug application, the current marketing of these products in the United States violate sections 301(d) and 505(a) of the Act (21 U.S.C. 331(d), 355(a)).

Several of the products listed above are also misbranded. Specifically, both Sunrise Pharmaceutical Aspirin 325 mg Enteric Safety Coated drug products (100 and 1000 tablets) are misbranded under sections 201 (n) and 502(a) and (f) of the Act because both products' labeling have the Reye's Syndrome warning as the third warning under the 'Warnings" section, whereas, under 21 CFR 201.315(h)(2), the Reye's Syndrome warning is required to be "the first warning statement under the heading 'Warnings'" (see also 21 CFR 201.315(h)(4)).

In addition, the following products are misbranded under 502(c) and 502(e)(1)(A)(iii) because the inactive ingredients are not listed in alphabetical order, as required under 502(e)(1)(A)(iii) and 21 CFR 201.66(c)(8):

- Sunrise Pharmaceutical, Aspirin, 325 mg, Pain Reliever Enteric Safety Coated, 100 Tablets
- Sunrise Pharmaceutical, Aspirin, 325 mg, Pain Reliever Enteric Safety Coated, 1000 Tablets
- Sunrise Pharmaceutical, Bisacodyl USP, 5 mg, Laxative, Enteric Sugar Coated, 100 Tablets
- Sunrise Pharmaceutical, Bisacodyl USP, 5 mg, Laxactive, 1000 Enteric Sugar Coated Tablets
- **(b)(4)** Bisacodyl Tablets, USP, 5 mg, Delayed-Release Tablets Enteric Coated, 100 Tablets
- **(b)(4)** Bisacodyl Tablets, USP, 5 mg, Delayed-Release Tablets Enteric Coated, 1000 Tablets
- **(b)(4)** Diphenhydramine HCL Capsules, USP, 50 mg, Antihistamine, 100 Capsules
- **(b)(4)** Diphenhydramine HCL Capsules, USP, 50 mg, Antihistamine, 1000 Capsules
- **(b)(4)** Diphenhydramine HCL Capsules, USP, 25 mg, Antihistamine, 1000 Capsules
- Sunrise Pharmaceutical, Aspirin, 81 mg, Pain Reliever Adult Low Dose, Enteric Safety Coated, 120 Tablets
- Sunrise Pharmaceutical, Aspirin, 81 mg, Pain Reliever Adult Low Dose, Enteric Safety Coated, 1000 Tablets
- Sunrise Pharmaceutical, Senna, 8.6 mg, Docusate Sodium, 50 mg, Natural Vegetable Laxative plus Stool Softener, 60 Tablets
- **(b)(4)** Natural Vegetable Laxative Plus Stool Softener, 100 Tablets
- **(b)(4)** Natural Vegetable Laxative Plus Stool Softener, 1000 Tablets
- **(b)(4)** Docusate Sodium, Stool Softener Plus Laxative, 100 Tablets
- **(b)(4)** Docusate Sodium, Stool Softener Plus Laxative, 100 Tablets

Furthermore, all of these products that do not list the inactive ingredients in alphabetical order--except the diphenhydramine HCL products--also have an inactive ingredients header under the "Drug Facts" that states "May contain the following inactive ingredients" (emphasis added). The use of "May contain" in the inactive ingredients header does not comport with the appropriate heading under 21 CFR 201.66(c)(8) and makes the product misbranded under 502(c) of the Act. Also, the use of "May contain" to list inactive ingredients indicates that there are inactive ingredients that may or may not be present in the product. Such labeling that lists all ingredients as potentially alternative ingredients is false and misleading and makes the product misbranded under 502(a) because it fails to identify which inactive ingredients are present in the product (See FDA's "Guidance for Industry Labeling OTC Human Drug Products", May 2009, for guidance on labeling inactive ingredients that may or may not be contained).

Also, for your information, the formatting of the "Drug Facts" section on several of your OTC products is inconsistent with the requirements under 21 CFR 201.66. For example, the "Aspirin, 325 mg, Pain Reliever Enteric Safety Coated, 1000 tablets" product does not have its "Drug Facts" header in larger font than the rest of the "Drug Facts" (see 21 CFR 201.66(d)(2).

Misbranding of bulk packaged finished OTC drug products intended for repackaging

In addition, based on the information collected during the inspection, you also manufacture the following OTC drugs that are finished OTC products shipped with bulk package labeling for repackaging, including but not limited to:

- Aspirin Film Coated White Tablets, 325 mg
- Aspirin Enteric Coated Orange Tablets, 325mg
- Phenylephrine Hydrochloride Film Coated Red Tablets, 5mg
- Phenylephrine HCL F/C Red Tablets, 10mg
- Bisacodyl E/C Orange Tablets, 5mg
- Chlorpheniramine Maleate Yellow Tablets 4mg
- Guaifenesin Caplets
- Guaifenesin & Dextromethorphan HBr. Caplets, 400mg & 20mg
- Chewable Aspirin Orange Flavor Tablets 81 Mg
- Diphenhydramine HCL Capsules, 50mg
- Diphenhydramine Hydrochloride Capsules, 25mg
- Aspirin Enteric Coated Yellow Tablets, 81 mg
- Senna & Docusate sodium F/C Orange Tablets, 8.6mg & 50mg
- Senna & Docusate sodium F/C Red Tablets, 8.6mg &50mg
- Aspirin Enteric Coated Peach Tablets, 81 mg

Based on documentation and bulk package labeling collected for the above products, the products are finished OTC drug products labeled for repackaging. As finished OTC drug products, the above OTC drug products once introduced into interstate commerce for repackaging, unless exempted under 21 CFR 201.150, must meet all drug labeling requirements described in section 502 of the Act (21 USC 352) and in 21 CFR 201, including the "Drug Facts" labeling requirements under 21 CFR 201.66. Based on documentation collected there is no evidence that the operators of the establishments where the drugs are to be repackaged are part of Sunrise Pharmaceuticals nor is there evidence that there are labeling agreements in place with such operators, and, in turn, neither exemption under 21 CFR 201.150(1) or (2), respectively, are met. Therefore, the above products, which only have bulk package labeling, are misbranded: (1) under section 502(c) of the Act because none of the outer container labeling contains "Drug Facts" required by 21 CFR 201.66; (2) under section 502(e)(1)(A)(iii) because the inactive ingredients are not listed; (3) under 502(f) of the Act because there are not adequate directions for use and warnings; and (4) under sections 502(a) and 201(n) of the Act because the bulk labeling is misleading by conveying the products are exempt from required FDCA labeling.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. We note that several deficiencies were cited in the August 2007 inspection and correction actions were promised. The current inspection found that promised corrective actions have not occurred and the same deficiencies exist at your firm. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. It is your responsibility to assure compliance with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute the drug products manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

We also request that you outline the action you are taking to discontinue the marketing of the unapproved drug products at your facility, or any other applicable drug which you may market. Also please note that if you are no longer marketing these products, you must update the Drug Listing files in accordance with 21 CFR 207.30(a)(2).

Your response should be sent to the following address: U.S. Food & Drug Administration, 10 Waterview Boulevard, 3rd Floor, Parsippany, New Jersey 07054, Attn: Sarah A. Della Fave, Compliance Officer.

Sincerely,

/s/

Diana Amador-Toro
Director, New Jersey District

Links on this page:

EXHIBIT 44

Vision Pharm, LLC 4/29/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Southeast Region
555 Winderley Place
Suite 200
Maitland, Florida 32751

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

FLA-10-17

April 29, 2010

Sander S. Busman
President & Chief Executive Officer
Vision Pharma, LLC
9180 Estero Park Commons Boulevard
Unit 1
Estero, FL 33928

Dear Mr. Busman:

On **(b)(4)** FDA issued a warning letter to **(b)(4)**. Inc. **(b)(4)** (copy attached). As explained more fully in that **(b)(4)**, certain drug products that **(b)(4)** has manufactured are new drugs that lack approved applications as required under the Federal Food, Drug, and Cosmetic Act (the Act). **(b)(4)** **(b)(4)**. These drug products include, but are not necessarily limited to:

- Colchicine Tablets, 0.6 mg
- Hyoscyamine Sulfate Tablets, USP, 0.125 mg
- Hyoscyamine Sulfate Orally Disintegrating Tablets, 0.125 mg
- Hyoscyamine Sulfate Sublingual Tablets, 0.125 mg

The above products are drugs within the meaning of section 201(g) of the Act, [21 U.S.C. § 321(g)] because, as demonstrated by their labeling, they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases. Further, they are "new drugs" within the meaning of section 201(p) of the Act [21 U.S.C. § 321(p)] because they are not generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested in their labeling. Under sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331 (d) and 355 (a)], a new drug may not be introduced into or delivered for introduction into interstate commerce unless an application approved by FDA under either section 505(b) or (j) of the Act [21 U.S.C. § 355(b) or (j)] is in effect for the drug. Based on our information, there are no FDA - approved applications on file for these drug products **(b)(4)**

Additionally, because the above prescription drug products are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions cannot be written for them so that a layman can use these products safely for their intended uses, as described in 21 C.F.R. § 201.5. Consequently, their labeling fails to bear adequate directions for their intended uses, causing them to be misbranded under section 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)]. Because the products lack required approved applications, they are not exempt under 21 C.F.R. § 201.115 from the requirements of section 502(f)(1) of the Act. The introduction or delivery for introduction into interstate commerce of these products without approved new drug applications violates section 301(a) and (d) of the Act [21 U.S.C. §§ 331(a) and (d)].

Further, as explained in the **(b)(4)**, the above drug products are adulterated, 21 U.S.C. 351(a)(2)(B), and thus your firm may not introduce or deliver them for introduction into interstate commerce, 21 U.S.C. § 331(a).

The violations cited in this letter are not intended to be an all-inclusive statement of violations that may exist in connection with your products. In particular, violations cited in this letter are not necessarily limited to drug products manufactured by Sunrise and may apply to all drug products that you market without FDA-approved applications. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure, and injunction. Other federal agencies may take this **(b)(4)** into account when considering the award of contracts.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the time within which you will complete the correction. If you no longer market the above products, your response should so indicate, including the reasons that, and the date on which, you

ceased production.

Your reply should be sent to U.S. Food & Drug Administration, 555 Winderley Place, Suite 200, Maitland, Florida, Attn: Winston R. Alejo, Compliance Officer.

Sincerely,

/s/

Emma R. Singleton
Director, Florida District

Enclosure

(b)(4)

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